# Conformational Analysis of Synthetic Neolignans Active Against Leishmaniasis, Using the Molecular Mechanics Method (MM2)

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**ABSTRACT:** Conformational analysis of 20 neolignans was performed to determine the most probable conformer that may fit the receptor. The molecular mechanics method (MM2) was employed to construct conformational maps in both a vacuum and a biological environment. Boltzmann's distribution among several local minima was calculated. © 1997 by John Wiley & Sons, Inc.
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**Keywords:** molecular mechanics; neolignans; conformational analysis; environment effect; active conformation

## Introduction

The majority of the drugs are flexible molecules with one or more single bonds about which free rotation can occur. Experimental techniques such as crystallography can determine only the most stable conformation.

When we are interested in drug–receptor interactions, the ''lock-and-key'' hypothesis can be considered. There is the possibility of the presence of several local minima in a conformational map. One of them can be active conformation.

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Calculations of geometry optimization can be performed by varying torsional angles around two or more single bonds in a molecule simultaneously. Total energies are calculated at each torsional angle. The total energies versus torsional angles can be plotted graphically. Thus the graph plotted is a contour map corresponding to a potential energy surface which consists of ''mountains'' and ''valleys.'' It provides information about positions of local minima and height of rotational barriers.

According to the ''lock-and-key'' hypothesis, any one of those conformations of minimum energy can be the active conformation if potential barriers among the valleys are not too large.

The conformational map is also useful for showing the flexibility of conformational change inside


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the valleys. This can be determined by the values of probability for each local minimum. A wide, shallow depression favors conformational flexibility more than a narrow, deep one. This is because the flexible molecules are not confined to the depth of the hole, but they can be spread among available energy levels.[1]

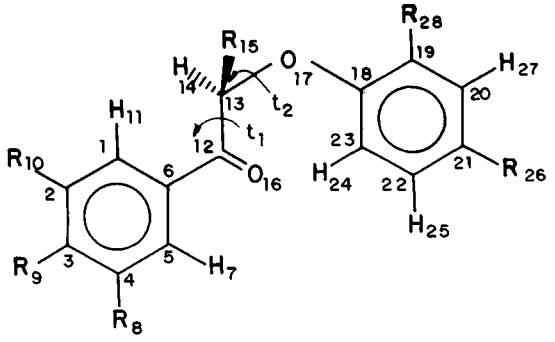
If the calculations of geometry optimization of drugs were performed under vacuum conditions, the results may or may not be very useful. When the drugs act in biological environments, there exist two types of solvent: water and nonpolar substances.

The presence of charged groups or dipoles within a flexible molecule affects its conformation, because two charges of opposite sign attract each other and the two groups tend to come close, whereas like charges repel each other and the two groups tend to move away from one another. This effect depends on the dielectric constant of the medium separating the two charges.

Many chemical reactions in biological systems are catalyzed by enzymes found in the cytoplasm of the cell. Because of the diversity of the composition in the biological medium, it is difficult to know what the effective dielectric constant is in the drug–receptor interaction.[2] The nonaqueous phase can be represented by globular proteins. A globular protein is a heavily folded sphere, with polar water molecules largely excluded from its center. A protein may therefore be treated as a region of low dielectric constant (usually 2–5) embedded in a surrounding medium of high dielectric constant (water, with 80 for the value of dielectric constant). In considering the association between an ion in solution and a charged group within a protein, the presence of this region of low dielectric constant has a marked effect on the effective dielectric constant of the medium between the ions. Schellman[3] applied the methods of classical electrostatics to this problem of ionic interaction near an interface between regions of high and low dielectric constant. When applied to the experimentally determined value of the association constant of chloride ion with serum albumin, a value of 28 for the effective dielectric constant was obtained.[4]

Neolignans are dimers from oxidative coupling of allyl and propenyl phenols that occur in the *Myristicaceae* and other primitive plant families. The *Virola* is the most representative *Myristicaceae* occurring throughout the Americas.[5, 6]

In 1970, initial studies of leaves of *Virola surinamensis* showed high efficacy in the blockage tests of penetration of cercarie of *Schistosoma mansoni* in mice. The active substances responsible for protection were isolated and identified as the natural neolignans, virolin and surinamensin (Fig. 1). Barata et al.[7] and Santos[8] synthesized 20 analogs of these active substances to determine the biological activity of neolignans. They were submitted to diverse biological tests and some of these showed activity against leishmaniasis, a tropical disease transmitted by mosquitos.




a) Virolin ; $R_8=H$, $R_9=R_{10}=R_{28}=-OCH_3$, $R_{15}=-CH_3$, $R_{26}=-CH=CH-CH_3$ (trans)

b) Surinamensin ; $R_8=R_9=R_{10}=R_{28}=-OCH_3$, $R_{15}=-CH_3$, $R_{26}=-CH=CH-CH_3$ (trans)

**FIGURE 1.** The natural neolignans, virolin (a) and surinamensin (b), were isolated from leaves of *Virola surinamensis,* and they showed biological activity against *Schistosoma mansoni.* $t_1$ and $t_2$ are the rotational angles.

The biological tests were made by Neal and others from the London School of Hygiene and Tropical Medicine.[9] The biological activity of some of the compounds studied by our group can be found in Santos's doctoral thesis,[8] but other data were obtained by personal communication from Neal's group. We do not know the values of the biological activities, but we do know if they are active or inactive.

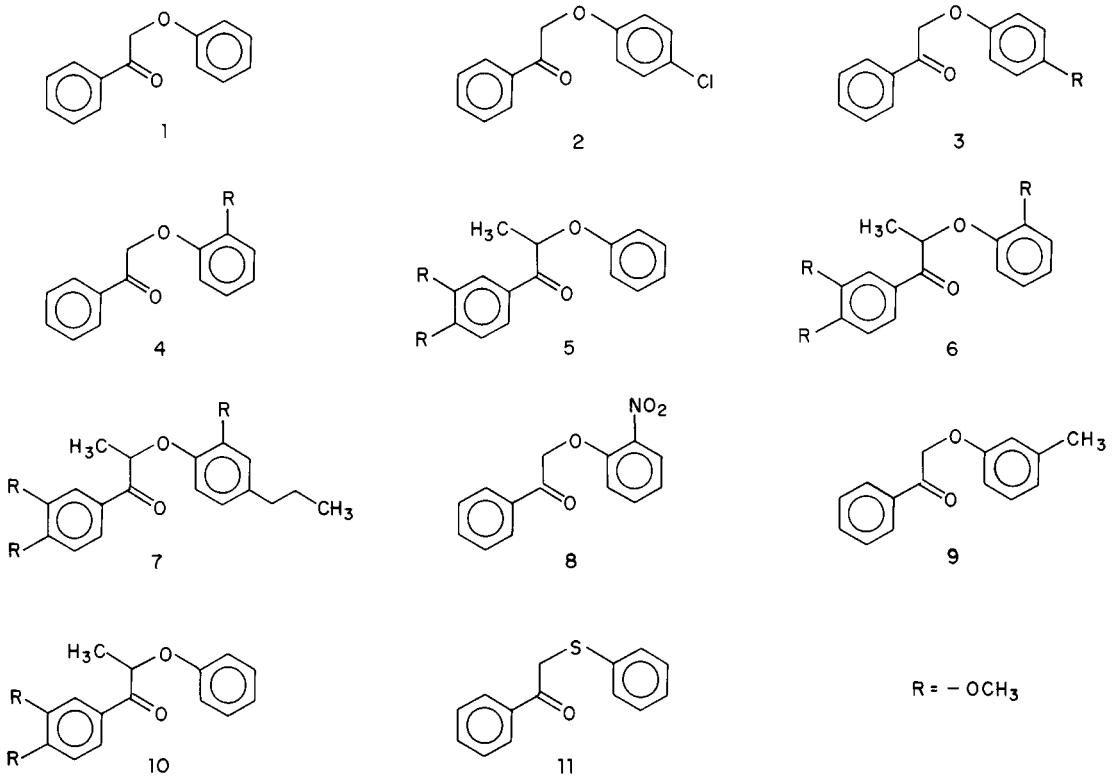
Nine molecules of these showed activity in vitro, and 11 showed inactivity. Scheme I shows inactive compounds (1 to 11), and Scheme II shows active ones (12 to 20).

In this work, we are interested in knowing the conformation of the neolignans and their related compounds that is essential to activity. There are as many stable conformations as local minima. However, only one of them may fit well with the receptor. We do not know the receptor conformation, but we can look for the most probable conformation to fit the receptor.

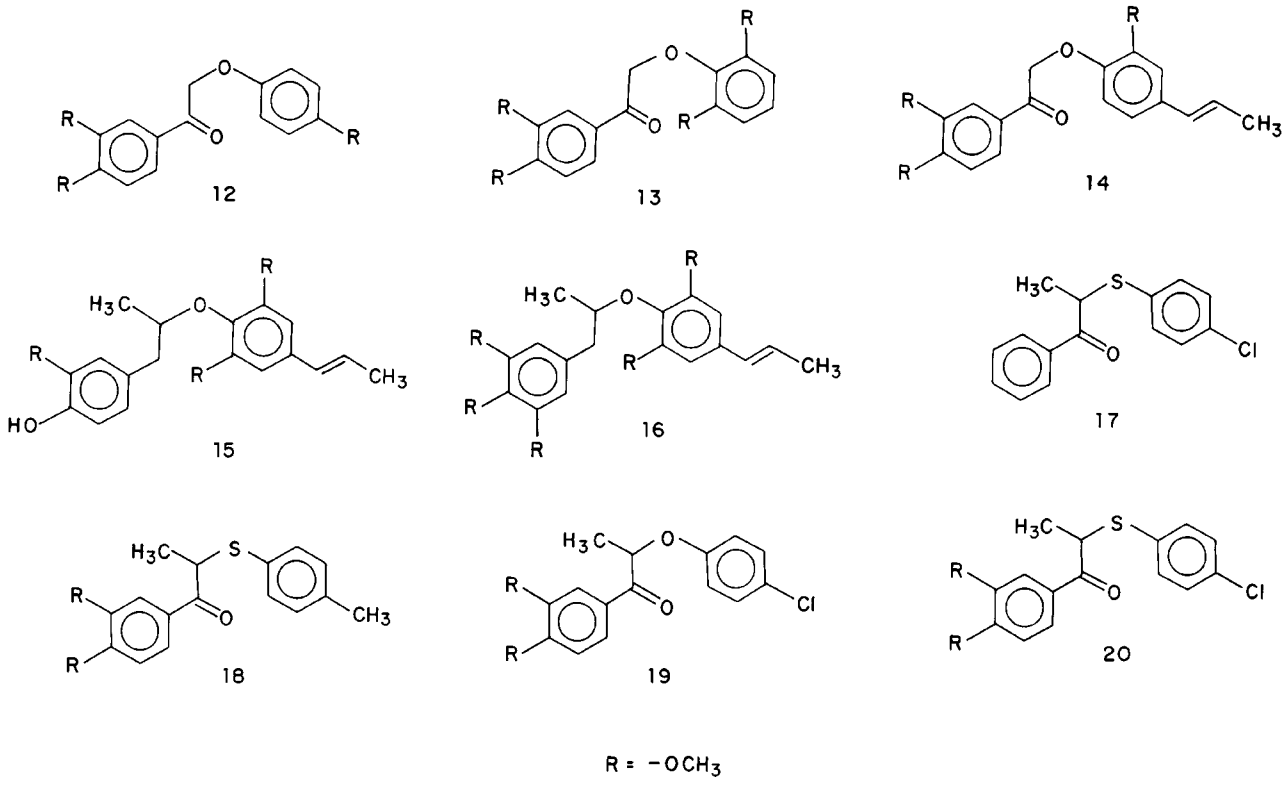
We first studied the effect of change in dielectric constant of the medium on conformation, calculating it in vacuum and then using the value of the dielectric constant of a biological environment.

## Methods

The molecular mechanics method (MM2)[10] was employed to calculate conformational maps. We used the 1987 force field together with some parameters of MM2'.[11] We also determined some parameters that were not previously known. These are listed in Tables I and II. These parameters were chosen and tested on molecules with known geometry, and contain fragments to which we could determine the MM2 parameters. Initially, we investigated the conformational map of compound 1. Both H(14)–C(13)–C(12)–C(6) and C(18)–O(17)–C(13)–C(12) dihedral angles (torsional angles $t_1$ and $t_2$ in Fig. 1, respectively) were varied simultaneously from 0° to 360° in 15° steps to generate 576 rotational conformers. Eight local minima were found. At each fixed $t_1$ and $t_2$, the geometries of the whole molecules (bond angles, bond lengths, and dihedral angles) were optimized. The MM2 parameters were kept unchanged during this optimization. For the other 17 molecules (2 to 14 and 17 to 20) that have the same basic structure as molecule 1 (see Schemes I and




**SCHEME 1.** Synthetic neolignans—inactivities against leishmaniasis.[6,7]




**SCHEME 2.** Synthetic neolignans—activities against leishmaniasis.[6,7]

II), the substituents were placed at each one of the eight minima of molecule 1. If a substituent had a rotation axis, it was rotated from 0° to 360° in 10° steps. A new set of local minima were found for each molecule. We named the local minima, A, B, C, D, E, F, G, and H, according to the values of torsional angles $t_1$ and $t_2$ in Figure 1. For example, for all the molecules, local minimum A corresponded to $t_1$ and $t_2$ near to 60°; local minimum B corresponded to $t_1$ near 150° and $t_2$ near 60°.

It was necessary to calculate completely new potential energy surfaces for molecules 15 and 16 because they have different basic structures from 1. Nine local minima were found in 15 and 16.

We first studied the effect of change in dielectric constant of the medium on conformation by calculating it in vacuum and then using the dielectric constant of the biological environment. The dielectric constant was changed in the input data of MM2. Following these calculations, we constructed the conformational maps for active molecules and performed probability calculations.

To know the probability of each minimum energy conformation, we associate each minimum the partition function $Z$:

$$Z_{conformational} = \sum_{(t_1, t_2)} \exp[-E_{(t_1, t_2)}/kT] \quad (1)$$

where $E_{(t_1, t_2)}$ is the calculated energy for a conformation defined by $t_1$ and $t_2$, $k$ is the Boltzmann constant, and $T$ is the temperature (37°C). The summation was taken over all calculated points between the local minimum point and $2kT$ above the minimum.[1]

The summation of the $Z_{conformational}$ of all the local minimum produced $Z_{total}$, where:

$$Z_{total} = \sum Z_{conformational} \quad (2)$$

The probability was obtained by the equation:

$$P = Z_{conformational}/Z_{total}. \quad (3)$$

## Results and Discussion

We optimized the geometry of inactive molecules 1 to 11, in both vacuum and biological

**TABLE I.**
**Torsional Parameters of the Molecular Mechanics Method. V1, V2, and V3 Are the First, Second, and Third Order Torsional Constants [C(ph) Is the C$sp^2$ in Benzene].**

| Torsional angles | Torsional parameters V1 | V2 | V3 | Source |
|---|---|---|---|---|
| C(ph) –C(ph) –C(C=O) –C($sp^3$) | 0.0 | 2.0 | 0.0 | Parametrized in this work |
| C(ph) –C(ph) –C(C=O) –O(=O) | 0.0 | 2.0 | 0.0 | ″ |
| C(C=O) –C($sp^3$) –O(–O–) –C(ph) | 0.0 | 0.0 | 0.403 | ″ |
| O(–O–) –C($sp^3$) –C(C=O) –C(ph) | 0.0 | 0.0 | 0.0 | ″ |
| S(–S–) –C($sp^3$) –C(C=O) –O(=O) | 0.0 | 0.0 | 0.0 | ″ |
| S(–S–) –C($sp^3$) –C(C=O) –C(ph) | 0.0 | 0.0 | 0.0 | ″ |
| C(C=O) –C($sp^3$) –S(–S–) –C(ph) | 0.0 | 0.0 | 0.483 | ″ |
| H –C($sp^3$) –S(–S–) –C(ph) | 0.0 | 0.0 | 0.500 | ″ |
| C(ph) –C(ph) –S(–S) –C($sp^3$) | 0.0 | 0.0 | 0.0 | ″ |
| H –C(ph) –C(ph) –S(–S–) | 0.0 | 16.250 | 0.0 | ″ |
| C(ph) –C(ph) –C(ph) –S(–S) | 0.0 | 15.0 | 0.0 | ″ |
| C($sp^3$) –C($sp^3$) –S(–S–) –C(ph) | −0.62 | 0.3 | 0.25 | ″ |
| C($sp^3$) –C($sp^3$) –C(C=O) –C(ph) | 0.0 | 0.0 | −0.11 | ″ |
| O(–O–) –C(ph) –C(ph) –O(–O–) | −2.0 | 16.25 | 0.0 | ″ |
| C(C=O) –C($sp^3$) –O(–O–) –C(ph) | 0.0 | 0.0 | 0.4 | ″ |
| C(ph) –C($sp^3$) –C($sp^3$) –O(–O–) | 0.0 | 0.0 | 0.0 | ″ |
| H(OH) –O(–O–) –C(ph) –C(ph) | 2.0 | 1.88 | −2.0 | ″ |
| O(–O–) –C(ph) –C(ph) –N($NO_2$) | 0.0 | 7.3 | 0.0 | *J. Comput. Chem.*, **10**, 635 (1989) |
| C(ph) –C(ph) –N($NO_2$) –O($NO_2$) | 0.0 | 5.0 | 0.0 | *Chem. Express*, **3**, 591 (1988) |
| C(ph) –C(ph) –C(ph) –N($NO_2$) | 0.0 | 7.3 | 0.0 | *Chem. Express*, **3**, 591 (1988) |
| H –C(ph) –C(ph) –N($NO_2$) | 0.0 | 7.3 | 0.0 | *Chem. Express*, **3**, 591 (1988) |
| C($sp^2$) –C($sp^2$) –C(ph) –C(ph) | −0.93 | 1.25 | 0.0 | *Chem. Express*, **3**, 591 (1988) |
| C($sp^3$) –O(–O–) –C(ph) –C(ph) | 0.0 | 9.2 | 0.0 | *Chem. Express*, **3**, 591 (1988) |
| H –C($sp^3$) –O(–O–) –C(ph) | 0.0 | 0.0 | 0.35 | *Chem. Express*, **3**, 591 (1988) |
| O(–O–) –C(ph) –C(ph) –C(ph) | 0.0 | 15.0 | 0.0 | *J. Comput. Chem.*, **10**, 635 (1989) |
| H –C(ph) –C(ph) –O(–O–) | 0.0 | 15.0 | 0.0 | *J. Comput. Chem.*, **10**, 635 (1989) |

media, using dielectric constants 1 and 28, respectively. Table III summarizes the results. Generally speaking, the order of conformational stability does not change significantly going from vacuum to biological medium. However, we can see some change in the stability of the conformations for some cases. For instance, molecules 5 and 6 show changes in their global minima. In case of molecule 5, conformation E is the global minimum at vacuum, but in the biological medium minimum B is more stable than E.

Conformation E has torsional angles $t_1$ and $t_2$ near 180°, and B has $t_1$ near 160° and $t_2$ near 60°. This means that B is a bent conformation, in which the two phenyl rings are close to each other (Fig. 2). The bent conformations are favored in a biological environment.

In the case of molecule 6, however, conformations F ($t_1 = 160°$ and $t_2 = 300°$) and C ($t_1 = 270°$ and $t_2 = 60°$) have the same probability in vacuum. These are more stable than B. In the biological medium, B is the global minimum. The two phenyl rings are especially closer in B than in C or F (see Fig. 2).

In Figure 2, the eight conformations of molecule 1 corresponding to the eight local minima A to H are shown. They are common to all molecules. We can see that conformations A and D are more stretched than the other six. Conformations B and G have phenyl rings closer than those of the others. Conformations C, F, E, and H have phenyl rings located at an intermediate distance compared with the others.

In Table III we notice that the most probable conformations of the majority of molecules, in the vacuum environment, are those with an intermediate distance between the phenyl rings (E, F, C, H). There are two molecules, 10 and 11, in which conformation B is the most probable.

In a biological medium, molecules 5 and 6, in addition to 10 and 11, also have conformation B as the most stable. The probability of bent conforma-

**TABLE II.**
**Bending, Out-of-Plane Bending and Stretching Parameters of Molecular Mechanics Method.[a]**

| | Bending parameters | | |
|---|---|---|---|
| Angles | $k_b$ (md · Å · rad$^2$) | $\alpha$ | Source |
| C($sp^3$) –O(–O–) –C(ph) | 0.77 | 113.6 | *J. Comput. Chem.*, **10**, 635 (1989) |
| O(–O–) –C(ph) –C(ph) | 0.60 | 120.0 | Parametrized in this work |
| N($NO_2$) –C(ph) –C(ph) | 0.50 | 114.0 | *Chem. Express*, **3**, 591 (1988) |
| O(=O) –N($NO_2$) –C(ph) | 0.50 | 118.0 | *Chem. Express.*, **3**, 591 (1988) |
| C(ph) –C(ph) –S | 0.38 | 119.0 | Parametrized in this work |
| C($sp^3$) –S –C(ph) | 0.72 | 96.3 | ″ |
| | Out-of-plane bending parameters | | |
| Angles | $k_b$ (md · Å · rad$^2$) | | Source |
| C(ph) –S | 0.05 | | Parametrized in this work |
| C(ph) –O(–O–) | 0.05 | | *J. Comput. Chem.*, **10**, 635 (1989) |
| C(ph) –N($NO_2$) | 0.05 | | *J. Comput. Chem.*, **10**, 635 (1989) |
| N($NO_2$) –C(ph) | 0.05 | | *Chem. Express*, **3**, 591 (1988); *Kagaku Gijitsu Kenkyucho Hokoku*, **86**, 141 (1991) |
| | Stretching parameters | | |
| Bond | $k_s$ (md · Å) | $l_0$ | Source |
| O –(–O–) –C(ph) | 5.00 | 1.43 | Parametrized in this work |
| N($NO_2$) –C(ph) | 5.00 | 1.48 | *Chem. Express*, **3**, 591 (1988) |
| C(ph) –C(ph) | 8.065 | 1.392 | Parametrized in this work |
| C(ph) –C(C=O) | 6.6 | 1.45 | ″ |
| C(ph) –S | 3.3 | 1.75 | ″ |

[a] $k_b$ is the bending force constant, $\alpha$ is the angle, $k_s$ is the stretching force constant, and $l_0$ is the bond length.

tions increases in a biological environment. These results suggest that we have to calculate conformational maps of the active molecules, using a value of 28 for the dielectric constant.

The conformational analysis of compounds with biological effect involves the search for active conformation. We produced conformational maps for all of the nine active molecules. The comparison between the permitted regions of the active molecules and the prohibited regions of the inactive ones gives us an idea about the active conformation.

**TABLE III.**
**Relative Decreasing Order of Stability for Inactive Molecules, in Vacuum and Biological Media (A, B, C, Etc., Are Local Minima).**

| | Relative decreasing order of stability | |
|---|---|---|
| Molecule | Vacuum | Biological medium |
| 1 | E > C > A > B > D | E > C > A > B > D |
| 2 | E > C > A > B > D | E > C > A > B > D |
| 3 | E > C > D > A > B | E > C > D > A > B |
| 4 | F > H > C > B > E > G > A > D | F > H > B = C = E > G = A > D |
| 5 | E > C > B > H > F = A > D > G | B > E > C > A > F > H > D > G |
| 6 | F = C > B > E > H > A > D > G | B > C > F > E > A > D > H > G |
| 7 | C > A > E > D > H > F | C > E > A > D > H > F |
| 8 | H > F > C > A = E | H > F > C > E = A |
| 9 | E = H > D > C > A | E = H > D > C > A |
| 10 | B > E > F > A > C > D > H > G | B > E > F > A > D > C > G > H |
| 11 | B > C > E > A > D | B > C > E > A > D |

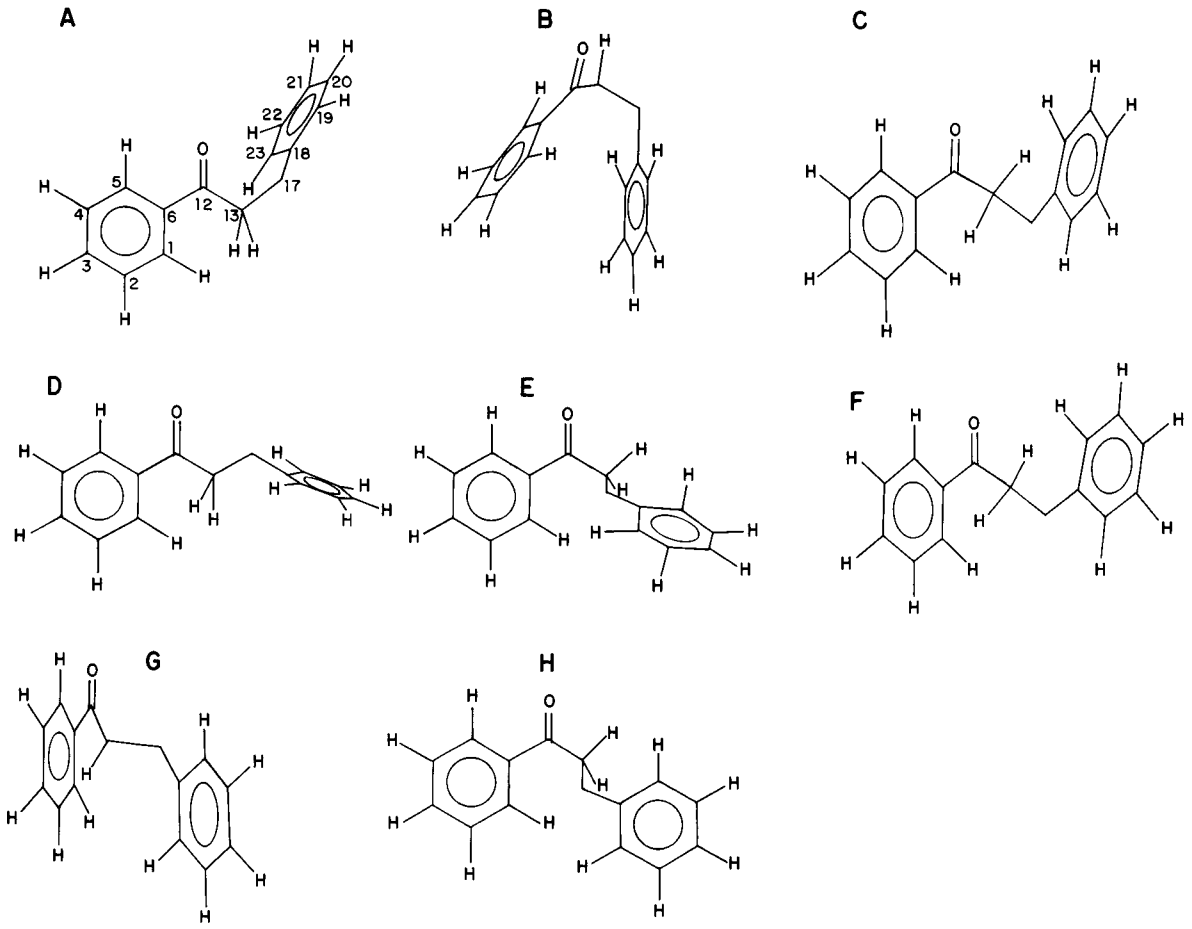



**FIGURE 2.** Eight calculated conformations corresponding to the eight local minima in a biological environment. The local minimum of molecule 1 shows that conformations A and D are more stretched than the remaining six. Conformations B and G have phenyl rings closer than those of the others. Conformations C, F, E, and H have the phenyl rings located at intermediate distance if compared to the others.

The compounds under study are flexible molecules and it was necessary to determine the probability of each minimum energy conformation. We calculated the partition function with eq. (1) at each minimum. Then, the probability was calculated with eq. (3). Tables IV and V show the probabilities and stabilities of the local minima of all the active molecules.

In molecules 12, 13, and 17, the order of stability and probability of the conformations are the same. The maps of molecules 12 and 13 show conformations A, C, D, E, F, H, and I. F, H, and I are enantiomers of C, E, and A, respectively. In all others in Tables IV and V we can see some inversion of the order. In molecule 14, conformations A and I are enantiomers; in the other molecules, there are no isomers present.

Figure 3 shows the conformational map of molecule 15, which is an example of a conformational map. We can observe clearly that the bottom of valley E is wider than that of H. This indicates that E is more probable than H, despite that hole E is less stable than H, according to Table IV. The same occurs with conformations A and D; both show the same probability, but D is more stable than A. This is because valley A is larger than D and this compensates for the effect of stability.

For molecule 16 it was impossible to obtain a conformational map due to technical difficulty. Table IV shows only its order of stability.

Molecule 14 presents an inversion of the order of conformational stability between C and F with the two different treatments. In molecule 18, the inversion occurs between conformations E and F

**TABLE IV.**
**Decreasing Order of Stability and Probability to Active Molecules.[a]**

| Molecule | Local minimum | *E* (kcal) | *P* (%) | Stability | Probability |
|---|---|---|---|---|---|
| 12 | A | 26.16 | 13 | | |
| | C | 25.90 | 23 | | |
| | D | 25.74 | 26 | E > D > C > A | E > D > C > **A** |
| | E | 25.27 | 38 | | |
| 13 | A | 32.19 | 16 | | |
| | C | 32.36 | 13 | | |
| | D | 31.92 | 21 | E > D > A > C | E > D > **A** > C |
| | E | 31.45 | 50 | | |
| 14 | A | 18.87 | 7 | | |
| | C | 18.43 | 19 | | |
| | D | 18.64 | 9 | | |
| | E | 17.83 | 19 | H > E > F > C > D > A | **H** > C = E > F > D > A |
| | F | 18.28 | 12 | | |
| | H | 17.78 | 34 | | |
| 15 | A | 20.55 | 1 | | |
| | B | 17.91 | 78 | | |
| | C | 19.80 | 4 | | |
| | D | 20.28 | 1 | | |
| | E | 19.60 | 10 | B > H > E > C > D > A > F > G > I | **B** ≫ E > **H** > C > **A** = D > F = **G** = **I** |
| | F | 25.11 | 0 | | |
| | G | 27.02 | 0 | | |
| | H | 19.41 | 6 | | |
| | I | 27.40 | 0 | | |
| 16 | A | 35.85 | | | |
| | B | 32.44 | | | |
| | C | 35.05 | | | |
| | D | 35.70 | | | |
| | E | 34.02 | | **B** > E > **H** > C > D > **A** > F > **G** > **I** | |
| | F | 40.18 | | | |
| | G | 41.13 | | | |
| | H | 34.72 | | | |
| | I | 41.71 | | | |

[a]It was impossible to obtain the order of probability of molecule 16 due to technical difficulty. The conformations represented in boldface are those that exist in only some of the active molecules, not in all active ones.

and between D and C. Molecules 19 and 20 also show some inversions.

The inversions observed in the conformational probability order confirm the importance of the inclusion of flexibility of the pharmacos.

The local minima that appear only in the inactive molecules can be discarded in the search for conformation that is essential for activity. In Tables III, IV, and V, we notice that there is no one inactive conformation absent in all active molecules. There are some local minima that do not appear among all the active molecules. It seems obvious that essential conformation to activity should be present in all the active compounds. Only four conformations, C, D, E, and F, are among these. Remember that conformers C and F are enantiomers in molecules 12 and 13, which is why F does not appear in Table IV in these molecules. If we eliminate the other minima—A, B, G, H, and I (boldface in Tables IV and V)—we observe that local minimum E is always the first or second in probability order. Thus, E could be the essential conformation for activity.

**TABLE V.**
**Decreasing Order of Stability and Probability of Active Molecules.**[a]

| Molecule | Local minimum | *E* (kcal) | *P* (%) | Stability | Probability |
|---|---|---|---|---|---|
| 17 | B | −1.14 | 53 | | |
| | C | 1.76 | 1 | | |
| | D | 1.32 | 2 | | |
| | E | −0.26 | 17 | B > F > E > D > C > G | **B** > F > E > D > C > **G** |
| | F | −0.40 | 27 | | |
| | G | 2.78 | 0 | | |
| 18 | B | 3.29 | 89 | | |
| | C | 7.81 | 0 | | |
| | D | 7.76 | 0 | | |
| | E | 5.93 | 5 | B > E > F > D > C = G > H | **B** > F > E > D = C = **G** = **H** |
| | F | 6.06 | 6 | | |
| | G | 7.81 | 0 | | |
| | H | 8.73 | 0 | | |
| 19 | A | 15.38 | 10 | | |
| | B | 14.38 | 55 | | |
| | C | 15.24 | 15 | | |
| | D | 16.97 | 1 | B > E > C > A > F > | **B** > C > E > **A** > F > |
| | E | 15.20 | 14 | > H > D > G | > **H** = D > **G** |
| | F | 16.15 | 4 | | |
| | G | 17.41 | 0 | | |
| | H | 16.75 | 1 | | |
| 20 | B | 4.62 | 82 | | |
| | C | 8.48 | 0 | | |
| | D | 8.28 | 0 | | |
| | E | 6.34 | 10 | B > E > F > D > C = G > H | **B** > E > F > C = D = **G** = **H** |
| | F | 6.55 | 8 | | |
| | G | 8.48 | 0 | | |
| | H | 9.26 | 0 | | |

[a]The conformations represented in boldface are those that exist in only some of the active molecules, not in all active ones.

The conformational map of molecule 15 (Fig. 3) shows that the E valley is large and wide, which enables the molecule to move around in the valley. A SAR study (structure–activity relationships) was applied to these compounds previously.[12] The active and inactive compounds were well separated when they were studied using conformation E. The methodology employed included pattern recognition methods and some new compounds were suggested for synthesis.

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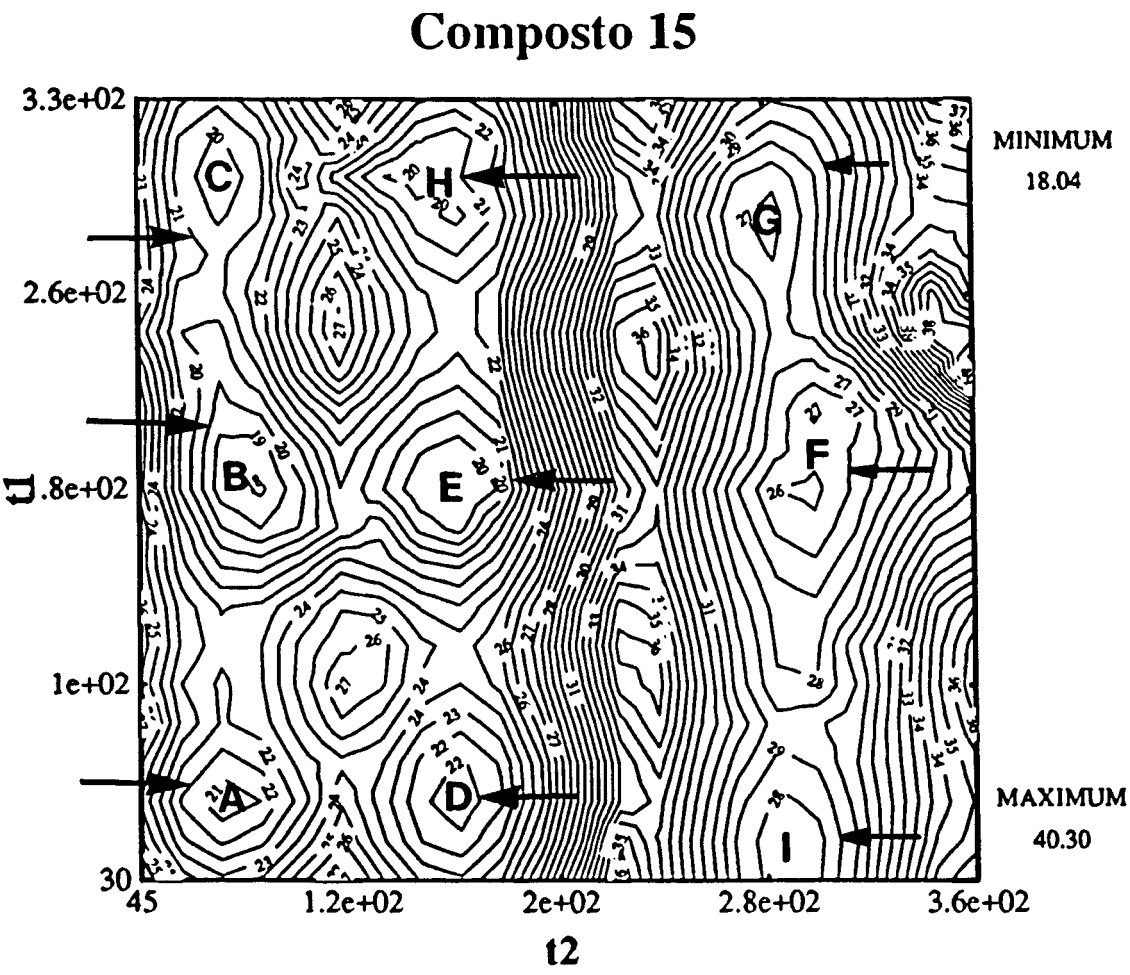


**FIGURE 3.** Conformational map to molecule 15. $t_1$ and $t_2$ represent the torsional axis (in degrees) shown in Figure 1. A, B, C, etc., are the local minima and the arrows indicate the limit of each minimum. The limits are calculated considering that each local minimum corresponds to the conformation of minimum energy ($E$) and the conformations with energy between $E$ and $E + 2kT$.


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